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Abstracts

EG-16. ABERRANT Myst4/Brpf1 SIGNALING MISDIRECTS REGIONAL NEUROGENESIS PROGRAMS, SUSTAINING EXPRESSION OF SELF-RENEWAL GENES IN PEDIATRIC BRAIN CANCERS

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The Myst family of acetyltransferase proteins has been shown to play important role in development and self-renewal, primarily through lysine acetylation on Histones H3 and H4. In neural development, Myst4 (Morf/KAT6B) has been found to be critical for self-renewal and for neuron generation in the developing nervous system and during adult neurogenesis. This chromatin modifier exists in a complex with Myst3 (Moz/KAT6A), the bromodomain factor Brpf1, which acts as a protein scaffold, targeting histone acetyltransferases to chromatin, as well as Inhibitor of Growth 5 (ING5) and Esa1-associated factor 6 (EAF6). Our laboratories have found alteration of these elements in pediatric brain cancers, suggesting a pathological role in abnormal neural progenitor growth. Exon-specific microarrays, DNA methylation studies and functional perturbation were performed to study the impact on tumor behavior. RNA interference in tumors and neural progenitors led to loss of H3K4acetylation in target genes and altered expression, including Spondin-1. Conversely, exogenous overexpression of targeting factors, such as Brpf1, enhanced expression of target genes, assessed by quantitative PCR analysis. Furthermore, expression of Myst3/4 and Brpf1 positively correlated with tumor malignancy markers in large patient cohorts, including Ki67, PCNA, and MELK, and with decreased overall survival. Assessment of direct functional relationships with tumor markers using ChIP-Seq approaches is currently being pursued to investigate direct Myst3/4/Brpf1-mediated promoter activity at known and novel target genes. These studies aim to elucidate the role of an important epigenetic mechanism in neurogenesis, the alteration of which may underlie global chromatin changes that contribute to tumor growth or initiation. Sustained progenitor growth may be suppressed by targeted therapies that disrupt these factors.